IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re PATENT APPLICATION OF

Robert B. DICKSON *et al.*

Application No. 09/936,333

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Examiner: Zachariah Lucas

Group Art Unit: 1648

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BRIEF ON APPEAL

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I. INTRODUCTION

This appeal is from an official action mailed August 10, 2005, finally rejecting claims 15, 16, 18, 19, and 34-36 of the above-identified patent application.

A. Real Party in Interest

The real party in interest for this appeal and the present application is the Georgetown University School of Medicine, by way of an Assignment recorded in the U.S. Patent and Trademark Office at Reel 012770, Frame 0529.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences known to Appellants, the Appellants' representatives or the Assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

C. Status of Claims

Claims 1-14 are **canceled**.

Claim 15 is **allowed**.

Claim 16 is **rejected** and is being **appealed**.

Claim 17 is **canceled**.

Claim 18 is **rejected** and is being **appealed**.

Claim 19 is **allowed**.

Claims 20-33 are **canceled**.

Claims 34-36 are **rejected** and are being **appealed**.

Claims 16, 18, and 34-36 stand rejected and are being appealed.

D. Status of Amendments

An amendment under 37 C.F.R. §1.116 was filed November 8, 2005, in response to the final official action mailed on August 10, 2005. The advisory action mailed November 30, 2005, indicated that for purposes of appeal, the amendment filed November 8, 2005, would be entered

of record, and that claims 15 and 19 would be allowed, and claims 16, 18, and 34-36 would remain rejected.

II. SUMMARY OF CLAIMED SUBJECT MATTER

The present application describes the applicants' discovery that human matriptase, a serine protease enzyme associated with tumor growth and invasion, is produced by human cells as an inactive single-chain form (zymogen) that is converted to a proteolytically active, two-chain form by cleavage at a specific site within the matriptase polypeptide. The applicants have characterized the active, two-chain form of the enzyme by describing its amino acid sequence (*e.g.*, see Fig. 9) and the location of the site of cleavage that activates the enzyme (*e.g.*, see Fig. 10), and by demonstrating that Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) binds to the two-chain form of matriptase and inhibits the active protease, but does not bind to the inactive, single-chain form (shown schematically in Fig. 14). The applicants have further demonstrated that monoclonal antibodies can be obtained that specifically recognize and bind the active two-chain form of human matriptase as an antigen, and have negligible affinity for the single-chain form of matriptase.

Claim 16 is the sole independent claim that is being appealed. Claim 16 is directed to "[a]n isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human." Description of the subject matter of claim 16 is found in specification in the following passages:

The application describes an object of the present invention as being "to provide an antibody or antibodies which recognizes and binds to SEQ ID NO:3 or a fragment thereof, SEQ ID NO:4 or a fragment thereof, to a single-chain (zymogen) form of matriptase or to a two-chain (active) form of matriptase," wherein "[p]referred antibodies are monoclonal antibodies and fragments thereof as well as chimeric, humanized or human antibodies." *See* page 14, lines 20-25. One of skill in the art would understand from the specification as a whole that the description in this passage of an antibody that binds "to a single-chain (zymogen) form of matriptase or to a two-chain (active) form of matriptase" is intended to include antibodies that bind specifically to the two-chain (active) form of matriptase and have little or no affinity for the single-chain (zymogen) form of matriptase. For example, the use of matriptase peptides or

matriptase proteins as antigens to obtain antibodies or antibody fragments that bind specifically to the two-chain (active) form of matriptase and not to the single-chain (zymogen) form of matriptase is described at page 35, line 11, to page 38, line 15, as well as in Example 5 on pages 89-91.

The term antibody is defined by the application as referring to "complete, intact antibodies, and Fab fragments and $F(ab)_2$ fragments thereof;" wherein the term "complete, intact antibodies" is intended to include "monoclonal antibodies such as murine monoclonal antibodies (mAb), chimeric antibodies and humanized antibodies," as described on page 21, lines 15-18.

The specification teaches that at the time the application was filed, "[t]he production of antibodies and the protein structures of complete, intact antibodies as well as antibody fragments (*e.g.*, Fab fragments and $F(ab)_2$ fragments) and the organization of genetic sequences that encode such molecules are well known and described, for example, in Harlow et al., ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1988). *See* page 21, lines 18-24.

Antibodies of the present invention are generally described as being useful for "the preparation of diagnostic or *in vivo* imaging means" of disclosed disease states (*see* page 45, lines 18-21).

Example 5 of the application describes a method for obtaining antibodies of the claimed invention that bind specifically to the active, two-chain form of human matriptase and have little or no affinity for the inactive, single-chain form of human matriptase (*see* pages 89-91). The method described in Example 5 comprises (a) preparing hybridomas that produce monoclonal antibodies that bind to the two-chain form of matriptase, and (b) screening the hybridomas to identify hybridomas that produce antibodies with negligible affinity for the single-chain form of matriptase (*see* page 90, line 7, to page 91, line 10). As described in Example 5, the inventors demonstrate that from a screen of about 80 hybridomas that produce monoclonal antibodies that bind to the two-chain form of human matriptase (*see* page 90, lines 7-14), two hybridomas (M69 and M123) were identified that produce antibodies that bind specifically to the antigenic two-chain form of matriptase and have negligible binding affinity for the single-chain form of matriptase (*see* page 91, lines 6-8).

Original claim 16 of the application is directed to "[a]n antibody or immunogenic fragment which selectively binds to the single-chain (zymogen) form of matriptase or two-chain (active) form of matriptase."

From the foregoing passages of the specification, one of skill in the art would understand that the application describes an isolated antibody or fragment thereof that selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human, in such a manner that it is evident that the applicants were in possession of the claimed invention at the time the application was filed.

III. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the final official action of August 10, 2005, the examiner identifies the following four grounds of rejection under 35 U.S.C. §112, first paragraph, for lack of written description, two of which apply to claims 16, 18, and 34-36, and two of which apply only to claim 36.

1. First ground of rejection - applies to claims 16, 18, and 34-36

Claims 16, 18, and 34-36 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not adequately describe the genus of antibodies that bind "with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human" to which the claims are directed. Although the application characterizes the antigenic two-chain (active) form of matriptase in terms of its primary structure (amino acid sequence), the activating cleavage site, and functional activities (ability to bind HAI-1 and proteolytic activity) relative to the single-chain (zymogen) form of matriptase, and describes two working examples of antibodies that bind with high affinity to different structural features of the two-chain (active) form of matriptase and have negligible affinity for the single-chain (zymogen) form of matriptase, the examiner alleges that the description of the claimed invention is insufficient because the application does not identify the specific epitopes of the two-chain (active) form of matriptase that are bound by the claimed antibodies, or a means of determining such epitopes, so as to allow those in the art to identify any particular structure that corresponds to an epitope present in the two-chain (active) form but not

in the single-chain (zymogen) form of matriptase. *See* page 7, lines 4-15, of the final official action mailed on August 10, 2005.

2. Second ground of rejection - applies to claims 16, 18, and 34-36

Claims 16, 18, and 34-36 are further rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not adequately describe a reproducible means for producing claimed antibodies M123 and M69, as no deposit or sequence is provided. The examiner further maintains that disclosure of a reproducible means for producing antibodies M123 and M69 would not overcome the rejection, since the description of antibodies M123 and M69 does not provide description "relevant to determining what other epitopes may be targeted to achieve the same function." *See* page 7, line 17, to page 8, line 2, of the final official action mailed on August 10, 2005.

3. Third ground of rejection - applies only to claim 36

Claim 36 is further rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to provide adequate description of a complex formed by the binding of the two-chain (active) form of a matriptase protein to any Kunitz-type serine inhibitor other than HAI-1. *See* page 8, lines 3-8, of the final official action mailed on August 10, 2005.

4. Fourth ground of rejection - applies only to claim 36

Claim 36 is also further rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description, because the application allegedly indicates that antibody M123 is able to bind to the two-chain (active) form of human matriptase and performs the function of the inhibitor HAI-1, but the application is not considered to adequately describe antibodies such as antibody M123 that bind to the two-chain (active) form of human matriptase and perform the function of HAI-1. *See* page 8, lines 8-13, of the final official action mailed on August 10, 2005.

IV. ARGUMENT

1. First ground of rejection - applies to claims 16, 18, and 34-36

In the final official action, the examiner alleges that rejected claims 16, 18, and 34-36 are directed to a genus of antibodies for which the description in the specification is not sufficient to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. The examiner acknowledges that the specification describes a reproducible method for obtaining the claimed antibodies, and identifies two working examples of the claimed antibodies, antibodies M123 and M69, that bind with high affinity and specificity to the two-chain (active) form of matriptase of a human, and have little or no affinity for the single-chain (zymogen) form of matriptase of said human. However, the examiner argues that the description of the claimed antibodies in the specification fails to support the entire scope of the claimed antibody genus. Specifically, the examiner considers the description of the claimed antibodies to be insufficient because it does not provide "any means of determining what epitope[s] these antibodies target so as to allow those in the art (to) identify any particular structure that may be targeted which structure would correspond to an epitope present in the two-chain but not in the zymogen form of matriptase." *See* page 7 of the official action. In the advisory action dated November 30, 2005, the examiner further stated that since the disclosure of two different examples of the claimed antibodies in the specification "provides no information as to the identification of other antibodies within the claimed genus, other than antibodies that bind to the specific epitopes targeted by these two specific antibodies, their disclosure fails to provide adequate support for the claimed genus." *See* page 2 of the advisory action.

The applicants' arguments in response to this ground of rejection are argued separately for (a) claims 16 and 34-36, and (b) claim 18.

(a) Argument with respect to the rejection of claims 16 and 34-36

The applicants submit that the application describes the antibodies or fragments thereof to which claims 16 and 34-36 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies. As discussed above in the Summary of Claimed Subject Matter, claim 16 is directed to an isolated antibody or

immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human. Claim 34 depends on claim 16, and specifies that the immunologically reactive fragment is selected from the group consisting of scFv, Fab, Fab', and $F(ab')_2$. Claim 35 depends on claim 16, and specifies that the single-chain form of matriptase comprises a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 4, and the two-chain form of matriptase is produced by cleavage of said single-chain form of matriptase. Claim 36 depends on claim 16, and specifies that the antibody or fragment thereof binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1 or a fragment thereof.

As discussed above, the examiner alleges that the specification does not satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, for claims 16 and 34-36, because it does not identify the epitopes that are targeted by the claimed antibodies or provide a means for determining such epitopes. *See* page 7 of the official action.

The amount and type of information required to satisfy the requirement for written description for a claimed invention under 35 U.S.C. §112, first paragraph, is dependent on the nature of the invention. *See* In re Smyth, 178 U.S.P.Q. 279 at 284 (CCPA 1973). With respect to claims directed to antibodies, it is established that the requirement for written description under 35 U.S.C. §112, first paragraph, for claims directed to antibodies that bind to a well-characterized antigenic protein can be satisfied solely by description of the antigenic protein with reference to distinguishing physical or structural parameters such as the molecular weight and/or the amino acid sequence of the antigenic protein.

> "In its Guidelines [regarding the requirement for written description under 35 U.S.C. §112, first paragraph], the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Guidelines,* 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with 112, 1, for a

> claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov/web/patents/guides.htm (*Application of Guidelines*)."

See Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir., 2002). Moreover, the PTO routinely issues patents with claims directed to antibodies that bind specifically to an antigenic protein that is disclosed and characterized by the corresponding application specifications, without requiring identification of the specific epitopes on the protein that are bound by the claimed antibodies, or without even requiring a demonstration that the claimed antibodies have been produced. The PTO's Written Description Guidelines, the examining practice of the PTO, and the Court of Appeals of the Federal Circuit, have recognized that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein.

In the present application, the applicants have disclosed and characterized an antigenic protein, the active, two-chain form of human matriptase, *e.g.*, in terms of its amino acid sequence (SEQ ID NO: 4), the location of the site of cleavage that activates the enzyme (*e.g.*, *see* page 78 and Figs. 9 and 10), and residues of the substrate-binding site (*see* pages 66-67). The application also demonstrates that the two-chain form of human matriptase is structurally and functionally distinct from the single chain form of matriptase, as evidenced by the disclosure that HAI-1 binds to and forms a complex with the two-chain form of matriptase, but does not bind to the single-chain form of human matriptase (*e.g.*, *see* page 78), and that the single-chain form of matriptase does not possess proteolytic activity (*e.g.*, *see* pages 66-67 and Fig. 14). Antibody fragments such as those of claim 34 are described in the application, *e.g.*, on page 21, lines 15-24. The nucleotide sequence of SEQ ID NO: 4 encoding the polypeptide of single-chain form of matriptase specified in claim 35 is described, *e.g.*, in Figure 9, and cleavage of said single-chain

form of matriptase to produce the two-chain form of matriptase as specified in claim 35 is described in the application, *e.g.*, on pages 78-79. Antibodies of the claimed invention that bind to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1 as specified in claim 36 are described, *e.g.*, on page 90, lines 7-14. As discussed above in the Summary of Claimed Subject Matter, an object of the invention is "to provide an antibody or antibodies which recognizes and binds to SEQ ID NO:3 or a fragment thereof, SEQ ID NO:4 or a fragment thereof, to a single-chain (zymogen) form of matriptase or to a two-chain (active) form of matriptase," and describes preferred antibodies as being "monoclonal antibodies or fragments thereof as well as chimeric, humanized or human antibodies" (*see* page 14, lines 20-25). In Example 5 of the application, the applicants describe reliable screening and assay procedures by which one of skill in the art can identify hybridoma clones that produce the claimed antibodies that bind specifically to the antigenic two-chain form of human matriptase and have little or no binding affinity for the single-chain form of matriptase. As described in the working example, the two-chain form of human matriptase present in a complex with HAI-1 was used as immunogen to produce approximately 80 hybridoma clones that produce antibodies that bind both the two-chain form of human matriptase complexed with HAI-1, and to the uncomplexed two-chain form of human matriptase. The approximately 80 hybridoma clones were then screened as described, and two disclosed hybridoma clones, M69 and M123, were identified that produce antibodies of the claimed invention that bind with high affinity and specificity to the antigenic two-chain (active) form of human matriptase and do not bind to the single-chain (zymogen) form of the protein. Differences in binding affinity of M69 and M123 for the non-boiled and boiled 95 kDa complex of HAI-1 and matriptase indicate that the two antibodies bind to different structural features on the antigenic two-chain form of matriptase. *See* Example 5, pages 89-91. The application thus both describes and discloses two working examples of the claimed antibodies, and one of skill in the art would reasonably expect to obtain additional examples of the claimed antibodies by routine screening using a screening method such as that which is described in the specification.

Moreover, as the application teaches that HAI-1 binds to and forms a complex with the two-chain form of human matriptase, but does not bind to the single-chain form of human matriptase, it would be clear to one of skill in the art that HAI-1 recognizes and binds to

structural features of the two-chain (active) form of human matriptase that are altered or absent on the single-chain (zymogen) form of matriptase, and which are exposed as additional antibody binding sites on the surface of the uncomplexed two-chain form of human matriptase. One of skill in the art therefore would reasonably expect that, at least with respect to claims 16, 34, and 35 (and claim 18, discussed below), the uncomplexed two-chain form of human matriptase can be used as immunogen in the disclosed method to produce the claimed antibodies with even higher yields of the claimed antibodies for a given number of hybridomas screened than the 1:40 ratio that was obtained in the disclosed example.

Furthermore, the application teaches that one of skill in the art can use known methods to prepare monoclonal or polyclonal antibodies that bind specifically to polypeptide fragments of the disclosed matriptase amino acid sequence (*see* pages 36-37). While the application describes a working example of the method wherein the complete two-chain form of human matriptase is used as immunogen for preparing the claimed antibodies, one of skill in the art at the time of filing would have been able to use well known and routine immunological methods for preparing antibodies that bind peptide fragments to identify specific structures (epitopes) bound by antibodies prepared by the exemplified method in which the entire two-chain form of matriptase is used as immunogen, for example, by competition screening.

The representative number of species within a genus of a claimed invention that must be disclosed to satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, depends on the nature and predictability of the field of the invention (*see* Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). As discussed above, decisions by the Court of Appeals of the Federal Circuit and PTO practice evidence a recognition that in view of the well defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the developed and mature state of antibody technology, an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein, even if the claimed antibodies have not been produced.

In accordance with the above, the applicants submit that the disclosure in the specification of two different antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase provides a representative number of species within the genus of the claimed invention in satisfaction of the requirement for written description under 35 U.S.C. §112, first paragraph. As pointed out above, the specification describes and characterizes the two-chain form of human matriptase in structural and chemical terms, *e.g.*, in terms of its amino acid sequence (SEQ ID NO: 4), the site of cleavage that activates the enzyme (*e.g.*, *see* page 78 and Figs. 9 and 10), and the amino acids that form the substrate-binding site (*see* pages 66-67) and catalytic site (*see* page 64). Since the application characterizes the antigenic two-chain form of human matriptase in chemical and structural terms that permit it to be clearly distinguished from the single-chain form of matriptase and from other proteins, and further describes two representative working examples of antibodies that bind to different structural features of the two-chain form of human matriptase and do not bind to the single-chain form of matriptase, one of skill in the art would reasonably have considered the applicants to have been in possession of the claimed invention at the time of filing. Accordingly, the applicants respectfully submit that the application satisfies the written description requirement of 35 U.S.C. §112, first paragraph, for claims 16 and 34-36.

(b) Argument with respect to the rejection of claim 18

The applicants respectfully submit that the application describes the antibodies to which claim 18 is directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

The examiner alleges that the specification does not satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, for claim 18, because it does not identify the epitopes that are targeted by the claimed antibodies or provide a means for determining such epitopes, as discussed above for claims 16 and 34-36. *See* page 7 of the official action.

The arguments presented above in support of the patentability of claims 16, 34, and 35 are also applicable with respect to claim 18. It is therefore requested that the arguments stated above with respect to the rejection of claims 16 and 34-36 also be applied and considered fully

with respect to the rejection of claim 18 for alleged non-compliance with the written description requirement of 35 U.S.C. §112, first paragraph.

Claim 18 is directed to an isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human as set forth in claim 16, wherein the antibody is a monoclonal antibody. As discussed above, the application describes a method for preparing monoclonal antibodies that selectively bind with high affinity to a two-chain (active) form of human matriptase, and have little or no affinity for the single-chain (zymogen) form of human matriptase. The application also describes two examples of the claimed monoclonal antibodies, M69 and M123, that bind with high affinity to different structural features of the two-chain (active) form of matriptase and have little or no affinity for the single-chain (zymogen) form of human matriptase (*see* Example 5).

As discussed above, decisions of the Court of Appeals of the Federal Circuit and the practice of the USPTO evidence the recognition that an application that describes and fully characterizes an antigenic protein in structural and chemical terms satisfies the written description requirement of 35 U.S.C. §112, first paragraph, with respect to claims directed to antibodies that bind specifically to the characterized antigenic protein, even if the claimed antibodies have not been produced. Accordingly, the applicants submit that the description of methods by which the claimed antibodies can be prepared, and the disclosure in the specification of two different monoclonal antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase and have little or no affinity for the single-chain form of matriptase, satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, of the genus of monoclonal antibody to which claim 18 is directed.

2. Second ground of rejection - applies to claims 16, 18, and 34-36

The applicants submit that the application describes the antibodies or fragments thereof to which claims 16, 18, and 34-36 are directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

In the final official action, the examiner further rejects claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, because the application is not considered to provide one of skill in the art with a reproducible means for producing the M123 and M69 antibodies for use in identifying the class of antibodies to which the rejected claims are directed. A declaration was submitted with the response to the final official action filed on November 8, 2005, declaring that hybridomas that produce antibodies M123 and M69 have been deposited under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the public availability of the deposited material will be irrevocably removed upon the granting of a patent, pursuant to 37 C.F.R. § 1.808, and the response amended the specification to provide the accession number, date, and description of the deposits, and the name and address of the depository, pursuant to 37 C.F.R. § 1.809(d). The applicants submit that to the extent that claims 16, 18, and 34-36 are rejected under 35 U.S.C. §112, first paragraph, for lack of written description with respect to provision of evidence of a reproducible means for obtaining antibodies M123 and M69, this ground of rejection is overcome by the declaration and amendment filed on November 8, 2005, regarding deposit of hybridomas that produce antibodies M123 and M69 under the terms of the Budapest Treaty.

3. Third ground of rejection - applies only to claim 36

The applicants submit that the application describes the antibodies or fragments thereof to which claim 36 is directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

In the final official action, the examiner further rejects claim 36 under 35 U.S.C. §112, first paragraph, because the application is not considered to provide adequate description of a two-chain form of a matriptase protein in a complex with any Kunitz-type inhibitor other than HAI-1. *See* page 9 of the official action. In the response to the final official action filed on November 8, 2005, claim 36 was amended to specify that the Kunitz-type inhibitor present in the complex with the two-chain (active) form of human matriptase protein is HAI-1. The applicants respectfully submit that to the extent that claim 36 is rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description of the two-chain form of matriptase protein in a complex of with a Kunitz-type inhibitor other than HAI-1, this ground of rejection is overcome

by the amendment of claim 36 to identify HAI-1 as the Kunitz-type inhibitor in the complex that is bound by the claimed antibody.

4. Fourth ground of rejection - applies only to claim 36

The applicants submit that the application describes the antibodies to which claim 36 is directed in a manner that satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the claimed antibodies.

Claim 36 is directed to an isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human as set forth in claim 16, wherein the antibody or fragment thereof binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1.

The examiner further rejects claim 36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description, because antibody M123 allegedly binds to the two-chain (active) form of human matriptase and performs the function of the inhibitor HAI-1, whereas the application is not considered to adequately describe antibodies that perform the function of HAI-1. *See* page 8, lines 8-13, of the final official action mailed on August 10, 2005.

The applicants respectfully submit that the examiner has incorrectly characterized the description of the activity and function of antibody M123 that is given by the specification. The specification does not describe antibody M123 as being capable of performing the function of the inhibitor protein HAI-1. As described in Example 5 of the specification, antibodies M69 and M123 were both obtained by screening hybridomas that were generated using the 95 kDa complex of HAI-1 and the two-chain form of human matriptase as immunogen, and both antibodies were shown to bind specifically to the purified two-chain form of human matriptase and not to the purified single-chain form of human matriptase (*see* page 91, lines 2-8). Both the M69 and M123 antibodies are described in the specification as working examples of antibodies that are capable of binding with high affinity to the two-chain (active) form of human matriptase protein that is present in a complex comprising HAI-1, and have little or no affinity for the single-chain (zymogen) form of human matriptase, as set forth in claim 36. Accordingly, the

applicants submit that the characterization of the antigenic complex of the two-chain form of human matriptase with HAI-1, the description of methods by which the claimed antibodies can be prepared, and the disclosure in the specification of two different antibodies, M69 and M123, that bind with high affinity to the two-chain form of human matriptase in complex with HAI-1 that have little or no affinity for the single-chain form of matriptase, satisfy the requirement for written description under 35 U.S.C. §112, first paragraph, of the genus of antibody to which claim 36 is directed. The applicants respectfully submit that to the extent that claim 36 is rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description because there is insufficient description of the binding of antibody M123 to the two-chain (active) form of human matriptase to perform the function of HAI-1, this ground of rejection is improper.

V. CONCLUSION

For at least the reasons discussed above, it is respectfully submitted that the description of the claimed invention provided by the application satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for rejected claims 16, 18, and 34-36.

For the above reasons, Appellants respectfully request this Honorable Board to reverse the rejection of the claims.

Respectfully submitted,

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VI. CLAIMS APPENDIX – CLAIMS ON APPEAL

16. An isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human.

18. The antibody or immunologically reactive fragment thereof of claim 16, wherein the antibody is a monoclonal antibody.

34. The antibody or immunologically reactive fragment thereof of claim 16, wherein the immunologically reactive fragment is selected from the group consisting of scFv, Fab, Fab', and $F(ab')_2$.

35. The antibody or immunologically reactive fragment thereof of claim 16, wherein said single-chain form of matriptase comprises a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 4, and the two-chain form of matriptase is produced by cleavage of said single-chain form of matriptase.

36. The antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising Hepatocyte growth factor activator inhibitor-1 (HAI-1) or a fragment thereof.

VII. EVIDENCE APPENDIX

NONE

VIII. RELATED PROCEEDINGS APPENDIX

NONE